II. REMARKS

Formal Matters

Claims 1-4, 6-8, and 10-22 are pending after entry of the amendments set forth herein.

Claims 1-8, 10-14, 19, and 20 were examined and were rejected. Claims 15-18, 21, and 22 were withdrawn from consideration.

Claim 1 is amended. The amendments to claim 1 were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Claim 1 is amended to include the language of claim 5. Accordingly, no new matter is added by these amendments.

Claim 5 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicant expressly reserves the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicant respectfully requests reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Ann Lam and Examiner Mark Shibuya for the courtesy of an in-person interview which took place on October 14, 2009, and which was attended by Examiner Lam, Examiner Shibuya, inventor Yadong Huang (by telephone), and Applicants' representative Paula A. Borden. During the interview, the rejections under 35 U.S.C. §112, first paragraph, were discussed. The amendments to the claims reflect the discussions which took place during the interview.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-4, 6-8, 10-14, 19, and 20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1-8, 10-14, 19, and 20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

Written description

The Office Action stated that Applicant does not disclose that any or all carboxyl-terminal truncated apoE fragments are markers of Alzheimer's Disease. Applicant respectfully traverses the rejection.

The instant specification provides ample written description of various carboxyl-terminal truncated apoE fragments. The instant specification provides molecular weight ranges of carboxyl-terminal truncated apoE fragments. Specification, paragraphs 0032-0034. The instant specification describes carboxyl-terminal truncations. Specification, paragraph 0030, and paragraph 00106. As such, those skilled in the art would

recognize that Applicant was in possession of the invention as claimed as of the priority date of the instant application.

Nevertheless, and solely in the interest of expediting prosecution, claim 1 is amended to include the language of claim 5. Claim 5 was not included in this rejection. As such, this rejection should be withdrawn.

Enablement

The Office Action stated that there are no data or other evidence submitted to support a correlation between a level of carboxyl-terminal truncated apoE and AD. Applicant respectfully traverses the rejection.

Comments regarding the examiner interview

As explained during the October 14, 2009 examiner interview:

- Full length apoE has not been report to be neurotoxic; instead, **carboxyl-terminal truncated** forms of apoE have been demonstrated to be neurotoxic;
- The instant specification describes a number of carboxyl-terminal apoE truncated polypeptides that are suitable for detection in a subject assay. For example, paragraph 0032 discusses the molecular weights of carboxyl-terminal apoE truncated polypeptides; paragraph 0034 discusses the truncations; and paragraph 0058 discusses examples of carboxyl-terminal apoE truncated polypeptides. Furthermore, as noted above, claim 1 is amended to recite that the carboxyl-terminal apoE truncated polypeptide includes amino acids 244-260 of apoE.
- Applicant provided **experimental data** in the specification, which data show that the ratio of carboxyl-terminal truncated apoE to full-length apoE in plasma of 20 Alzheimer's Disease patients was significantly higher than the ratio in normal (age-matched, non-demented) control individuals. The results are shown in **Figure 1**, and are described in Example 1. Similar results were obtained from a repeat study with additional patient samples and control samples. **Specification, paragraphs 106-109**.

The law regarding enablement

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

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[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

To comply with 35 U.S.C. §112, first paragraph, a specification need only enable a skilled artisan to make and use the claimed invention without undue experimentation. Accordingly, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue." One way to determine if undue experimentation is required is to analyze the subject specification in light of the *Wands* factors:[2] (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. However, all of the factors need not be reviewed when determining whether a disclosure is enabling.[3]

Applicant respectfully submits that when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, claims 1-8, 10-14, 19, and 20 recite subject matter that is adequately described in the specification in such a way as to teach a skilled artisan how to make and use the claimed invention without having to practice undue experimentation. An analysis of the *Wands* factors is provided below.

Amount of guidance provided

The instant specification provides at least the following:

a) a description of carboxyl-terminal truncated apoE (Specification, paragraphs 0027-0035);

b) a description of how to separate carboxyl-terminal truncated apoE from full-length apoE (Specification, paragraphs 0036-0049);

c) a description of various methods of detecting carboxyl-terminal truncated apoE (Specification, paragraphs 0050-0056);

d) a description of how to determine the proportion of carboxyl-terminal truncated apoE in a sample (Specification, paragraphs 0057-0062);

e) a description of antibodies that could be used in a claimed method, and how to prepare such antibodies (Specification, paragraphs 0063-0084);

f) a description of the level of carboxyl-terminal truncated apoE that would be expected to be diagnostic of Alzheimer's Disease (AD) (Specification, paragraphs 0092-0096); and

g) a **working example** of association of carboxyl-terminal truncated apoE levels with AD (Example 1; paragraphs 00106-00109).

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[2] *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)

Thus, those skilled in the art could readily and without undue experimentation, carry out a subject method as claimed.

Presence of working examples

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[4] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[5]

Nevertheless, the instant specification provides a working example. The instant specification describes a study in which plasma samples from 20 AD patient and 20 age-matched non-demented controls were analyzed by western blotting using antibody specific for full-length human apoE and antibody specific for C-terminal apoE (which does not recognize carboxyl-terminal truncated apoE).

As described in paragraph 00108 of the instant specification, and as shown in Figure 1 of the instant application, the ratio of the C-terminal truncated apoE to full-length apoE was significantly higher in AD patients than in age-matched non-demented controls.

Furthermore, as described in paragraph 00109 of the instant specification, similar results were obtained in a repeat study in which 80 more samples were included. The results demonstrated that the ratio of the C-terminal truncated apoE to full-length apoE was significantly higher in AD patients than in age-matched non-demented controls.

The quantity of experimentation necessary

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[6]

As the court explained[7]:

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[3] See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).
[4] In re Borkowski, 164 USPQ 642,645 (CCPA 1970).
[5] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).
[6] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
[7] *In re Wands* 8 USPQ 2d at 1404

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[8]

The claimed method requires **detecting a level of carboxyl-terminal truncated apoE**. The only experiments, if any, that need be performed to enable the entire scope of the claim are those that involve detecting carboxyl-terminal truncated apoE in an aqueous sample. The instant specification provides ample description as to how to carry out such detection. As described in the instant specification, detecting carboxyl-terminal truncated apoE is typically carried out using an antibody-based assay. Antibody-based assays are well known in the art. Since any such experiments would be routine in nature, no undue experimentation would be required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the level of carboxyl-terminal truncated apoE, and since this would only require use of methods that are well within the skill level of those of ordinary skill in the art, no undue experimentation is necessary.

Predictability in the art

The Office Action stated that the art of diagnosing a disease, such as AD, by detecting the presence or level of a biological molecule as a marker "is highly complicated as it involves an understanding of complex biological pathway." Office Action, page 4. This is incorrect.

There is no need to understand any complex biological pathways in order to carry out a subject method as claimed. All that is required is that one detect a level of carboxyl-terminal truncated apoE. The instant specification tells how to do this.

The Office Action stated that "given that those in the art have recommended against the use of apoE genotyping to predict the development of or to diagnose Alzheimer's disease … this appears to raise the question

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[8] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

as to why carboxyl-terminal apoE (in general, or the specific fragment of 244-260 of apoE) would be a reliable marker of the disease." Office Action, page 4. The Office Action asked "why would detection of carboxyl-terminated apoE be a diagnostic indicator of Alzheimer's disease when the full length apoE or its genotyping is not, as appears to be the conclusion of experts in the field?" Office Action, bridging sentence, pages 4-5.

Applicant is not required under 35 U.S.C. §112, first paragraph, to explain why unrelated methods do not work. Applicant has provided ample enablement for a method of diagnosing AD based on detection of carboxyl-terminal truncated apoE. Applicant is not required under 35 U.S.C. §112, first paragraph, to explain why others' methods are not effective.

Conclusion as to the rejections under 35 U.S.C. §112, first paragraph

Applicant submits that the above-discussed rejections under 35 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

III. CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GLAD-281.

Respectfully submitted,
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Date: November 16, 2009

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